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SOLID BICARBONATE DIALYSIS AGENT

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[There are no amendments to this patent.]

Abstract

Problem

To provide a single-pack solid bicarbonate dialysis agent that can be prepared as a high-concentration solution without forming insoluble carbonate salts and that has an excellent pH and sugar stability.

Means to solve

A solid bicarbonate dialysis agent that comprises an electrolyte composition containing a calcium salt, a pH control agent, sodium bicarbonate and, optionally, glucose, the electrolyte composition additionally containing a citrate salt, and forms solutions with essentially no precipitate.

Claims

1. A solid bicarbonate dialysis agent characterized by comprising an electrolyte composition containing a calcium salt, a pH control agent, sodium bicarbonate and, optionally, glucose, the electrolyte composition additionally containing a citrate salt, and forms solutions with essentially no precipitate.

2. A solid bicarbonate dialysis agent characterized by comprising an electrolyte composition containing a calcium salt, a pH control agent, sodium bicarbonate and, optionally, glucose, the electrolyte composition additionally containing a citrate salt, and being able to be adjusted to a solid dialysis agent concentration of about 2-15%, and is stable for more than 24 h.

3. The solid bicarbonate dialysis agent described in Claim 1 or 2, characterized by the citrate salt being sodium citrate.

4. The solid bicarbonate dialysis agent described in any of Claims 1-3, characterized by the pH control agent being at least one solid organic acid chosen from the group consisting of citric acid, malic acid, glucono-δ-lactone, adipic acid, succinic acid and tartaric acid.

5. The solid bicarbonate dialysis agent described in any of Claims 1-4, characterized by the citrate ion concentration being 1-4 times (equivalent ratio) that of the calcium ion.

6. The solid bicarbonate dialysis agent described in any of Claims 1-5, characterized by the pH ranging from weakly acidic to neutral pH in solution.

7. The solid bicarbonate dialysis agent described in any of Claims 1-6, characterized by being in single-pack form.

8. The solid bicarbonate dialysis agent described in any of Claims 1-6, characterized by being in twin-pack form comprising agent A, containing at least a calcium salt and citrate salt but not a bicarbonate salt, and agent B, containing at least a bicarbonate salt but not a calcium salt or citrate salt.

9. A packaged solid dialysis agent obtained by packaging a single-pack solid dialysis agent described in any of Claims 1-5 or a twin-pack solid dialysis agent described in Claim 8 characterized by using a packaging material containing aluminum or silicon oxide with a moisture permeability (40°C, 90% RH) below 2.0 g/cm^2·24 h.

10. A bicarbonate dialysis solution characterized by being obtained by dissolving the solid bicarbonate dialysis agent described in Claims 1-8 to a concentration of about 2-20% and containing essentially no precipitate.

Detailed explanation of the invention

[0001]

Technical field of the invention

The present invention concerns solid bicarbonate dialysis agents for making bicarbonate dialysis solutions. The solid bicarbonate dialysis agents of the present invention may be in single-pack or twin-pack form.

[0002]

In this specification, % means wt%.

[0003]

Prior art

Calcium salt-containing bicarbonate dialysis agents widely used currently have the following composition:

[0004]

Na^+	120-150	mEq/L
K^+	0.5-3.0	mEq/L
Ca^{2+}	1.5-4.5	mEq/L
Mg^{2+}	0-2.0	mEq/L
Cl^-	90-135	mEq/L
HCO_3^-	20-35	mEq/L
CH_3COO^-	2.0-12	mEq/L
Glucose	0-2.5	g/L

In general, they are in twin-pack form of a highly concentrated agent A comprising a calcium salt-containing electrolyte composition of sodium chloride, potassium chloride, calcium chloride, magnesium chloride and sodium acetate, a pH control agent such as acetic acid or hydrochloric acid, and, optionally, glucose, and an agent B containing sodium bicarbonate as a concentrated solution or powder.

[0005]

Recently, the packaging form and weight of the highly concentrated agents A and B have caused significant problems. The highly concentrated dialyzing fluids are conventionally contained in a polyethylene container, and the container size (10-20 L) causes problems in regard to transportation cost, storage space in hospitals, disposal of used polyethylene containers, etc. Problems in transporting and handling in hospitals caused by the heavy weight are also noted.

[0006]

To overcome such problems, making the dialyzing agents in powder form has been considered. Currently, for agent A, the dry granulation process involving the mixing of electrolyte compositions, pulverization and granulation under high pressure; the wet granulation process involving the mixing of electrolyte compositions with water, granulation and drying; the spray drying process, etc., have been developed. On the other hand, agent B is a single composition, thus powder preparations have been used.

[0007]

However, even in powder form, they are divided into two packs of agent A and B as in the case of solutions. Thus, in terms of handling, there is not much improvement. For simplified handling in hospitals and dialyzing fluid feed systems, the single-pack chemical system was developed. For example, in Japanese Kokai Patent Application No. Hei 03[1991]-74331, the chemicals are divided into a group containing a calcium component but not sodium bicarbonate and a group containing sodium bicarbonate but not a calcium component, and the former is granulated with the addition of acetic acid as a pH control agent and mixed to give a dialyzing agent. In Japanese Kokai Patent Application No. Hei 06[1994]-335528, a first agent containing an electrolyte composition and a solid acid and a second agent containing sodium bicarbonate, an electrolyte composition and glucose are mixed to obtain a dialysis agent. In Japanese Kokai Patent Application No. Hei 06[1994]-335527, dialysis agents are prepared by spray coating of sodium chloride with solutions of a first group containing a calcium salt, magnesium salt and solid organic acid, a second group containing potassium chloride, sodium acetate and glucose, a third group containing sodium bicarbonate, and then glucose. However, they all have problems. For example, in Japanese Kokai Patent Application No. Hei 03[1991]-74331, sodium bicarbonate reacts with the volatile acetic acid, causing changes in pH and leading to a loss in components and the ready formation of insoluble carbonate, resulting in stability problems. In Japanese Kokai Patent Application No. Hei 06[1994]-335527, the calcium salt and magnesium salt are physically covered by mutually nonreactive glucose, etc., which is not sufficient for suppressing the reactivity of the calcium salt and magnesium salt with sodium bicarbonate. Furthermore, an alkali and glucose are in contact in layers and a glucose solution is used for granulation and drying, and degradation of glucose may occur leading to discoloration and problems in long-term storage. Also, with dissolution of the alkaline sodium bicarbonate and then an acid, carbonate salts may precipitate readily. In Japanese Kokai Patent Application Nos. Hei 06[1994]-335527 and Hei 06[1994]-335528, calcium salt and sodium bicarbonate are separated into different groups, thus their contact may occur.

[0008]

As described above, single-pack solid dialysis agents containing both agents A and B have been researched and developed, but stability is a concern. To avoid precipitation of carbonate salts during the preparation of dialyzing fluids, currently, dissolution is made directly to the dialysis fluid concentration (about 1%) or lower. Namely, concentrated solutions such as commercially available dialysis fluids are very difficult to store for long periods.

[0009]

Furthermore, because the calcium and magnesium included in the dialysis fluid form insoluble carbonate salts and gradually precipitate in the dialysis fluid feeder and tubes, cleaning of the dialysis fluid feeder and tubes with acetic acid is necessary every day or every few days after use.

[0010]

Problems to be solved by the invention

It is the object of the present invention to provide single-pack or twin-pack, especially single-pack solid bicarbonate dialysis agents comprising electrolyte compositions, pH control agents, sodium bicarbonate and, optionally, glucose, which can be made into concentrated solutions without the formation of insoluble carbonate salts during dissolution or even after long-term storage, with excellent pH and sugar stability.

[0011]

Means to solve the problems

As a result of an extensive study of ways to solve such problems, the present inventors were able to prepare concentrated fluids conventionally difficult in making single-pack solid dialysis agents, by adding a citrate salt such as sodium citrate to the formulation.

[0012]

The present invention concerns solid bicarbonate dialysis agents that comprise an electrolyte composition containing a calcium salt, a pH control agent, sodium bicarbonate and, optionally, glucose, the electrolyte composition additionally containing a citrate salt, and form solutions with essentially no precipitate.

[0013]

The present invention also concerns solid bicarbonate dialysis agents that comprise an electrolyte composition containing a calcium salt, a pH control agent, sodium bicarbonate and, optionally, glucose, the electrolyte composition additionally containing a citrate salt, can be adjusted to a solid dialysis agent concentration of about 2-15% (w/v), and are stable for more than 24 h.

[0014]

Even in single-pack form, the solid bicarbonate dialysis agents of the present invention do not form precipitates during dissolution, thus dialysis fluid preparation is easy. Also, for twin-

pack equipment already existing in hospitals, the dialysis agents of the present invention may be made into twin-pack preparations comprising agent A containing the calcium salt and magnesium salt but not bicarbonate salt and agent B containing bicarbonate salt but not the calcium salt or magnesium salt.

[0015]

The single-pack or twin-pack solid bicarbonate dialysis agents of the present invention can be used as bicarbonate dialysis fluids after diluting the concentrated fluids to the desired concentration.

[0016]

Embodiments of the invention

The solid bicarbonate dialysis agents of the present invention are favored in single-pack or twin-pack form because the calcium salt such as calcium carbonate is not precipitated when made into a concentrated fluid. The dissolved concentration of the preparations of the present invention may vary according to the amount of sodium bicarbonate used, while it is about 2-20%. The concentrated solution stability may vary according to temperature, calcium salt content, sodium bicarbonate content and citrate salt content and their ratio, while precipitation does not occur for more than 24 h at 2-15% concentrations. the preferred concentration of the concentrated solutions of the present invention is 5-15%, more preferably 10-15%.

[0017]

In the dialysis agents of the present invention, sufficient citrate salt is added to prevent the reaction of calcium in the electrolyte composition with sodium bicarbonate, thus no insoluble carbonate salts are formed during dissolution, even after long-term storage, and solutions of about 2-20% can be prepared. Also, the concentrated solution may be diluted to an optimum concentration and used for bicarbonate dialysis fluid. The citrate salt content suitable for preventing calcium carbonate precipitation is 1-4 times the amount of citrate ions (including citrate ions from citric acid present as a pH control agent) to (equivalent ratio) calcium ions.

[0018]

In the preparations of the present invention, the pH control agent used is at least one physiologically allowable solid organic acid such as citric acid, malic acid, glucono-δ-lactone, adipic acid, succinic acid, or tartaric acid, while preferred pH control agents are citric acid and malic acid.

[0019]

The electrolyte compositions of the present invention can be chosen from sodium chloride, potassium chloride, magnesium chloride, calcium chloride, citrate salts, sodium bicarbonate, sodium acetate, potassium acetate, potassium bicarbonate, calcium gluconate, calcium citrate, sodium lactate, calcium lactate, etc.

[0020]

The citrate salt is at least one alkali metal salt or alkaline-earth metal salt chosen from citrate salts of sodium, potassium, calcium and magnesium, e.g., trisodium citrate, disodium monohydrogen citrate, sodium dihydrogen citrate, potassium dihydrogen citrate, calcium citrate, magnesium citrate, etc.

[0021]

The calcium salts that can be included in the electrolyte compositions are, e.g., calcium chloride, calcium citrate, calcium gluconate, calcium acetate, calcium lactate, etc.

[0022]

Preferred electrolyte compositions are sodium chloride, potassium chloride, magnesium chloride, calcium chloride, sodium bicarbonate and sodium citrate, and the compositions may also contain glucose and acetate salts such as calcium acetate, sodium acetate, etc. the preferred amount of electrolyte compositions compounded should be in the range given below after dilution to the desired concentration and can be determined appropriately by those skilled in the art. The dilution of concentrated fluids of the solid dialysis agents of the present invention to desired concentrations can be illustrated by the concentrations shown below.

[0023]

Na^+	120-150	mEq/L
K^+	0.5-3.0	mEq/L
Ca^{2+}	1.5-4.5	mEq/L
Mg^{2+}	0-2.0	mEq/L
Cl^-	90-135	mEq/L
HCO_3^-	20-35	mEq/L
Citrate ion	1.5-18	mEq/L
Acetate ion	0-12	mEq/L
Glucose	0-2.5	g/L

Within the range of no metabolic effects caused by excess citric acid, the amount of citrate ion compounded may be more than 4 times the amount of Ca^{2+}, to above 18 mEq/L.

[0024]

Especially preferred dialysis fluids contain about 30-40 mEq/L of combined citric acid, acetic acid and bicarbonate, and according to this value, the content of citrate salt, acetate salt, etc., is determined appropriately.

[0025]

Preferably, the solid bicarbonate dialysis agents of the present invention are packaged with packaging materials containing aluminum or silicon oxide, with a moisture permeability (40°C, 90%RH) below 2.0 $g/cm^2 \cdot 24$ h.

[0026]

The preparations of the present invention can be obtained by simple mixing of all the raw materials. However, considering enhancement of stability, it is desirable that the calcium salt and magnesium salt are granulated with an electrolyte composition other than sodium bicarbonate and separated from the sodium bicarbonate particles. It is further preferred that the calcium salt and magnesium salt are coated with sodium citrate, sodium acetate, sodium chloride, etc., to prevent direct contact with sodium bicarbonate. For example, at least one core chosen from the group consisting of sodium chloride, potassium chloride, etc., is covered with an inner layer of calcium salt, magnesium salt, etc., then a sodium citrate outer layer, and the resulting coated granules are mixed with a solid acid pH control agent and sodium bicarbonate and, if needed, mixed further with glucose.

[0027]

Considering carbon dioxide formation via decomposition of sodium bicarbonate and glucose stability, the electrolyte compositions should be dry or in anhydrous form. To maintain component uniformity in the mixed preparations, all particles should be about the same. More preferably, particles sorted by size should be used.

[0028]

The solid bicarbonate dialysis agents of the present invention may be in the form of laminates disclosed in Japanese Kokai Patent Application No. Hei 06[1994]-335527. In such case, the citrate salt may be compounded in the organic acid-containing layer, organic acid-free layer or interlayer. The citrate salt may be compounded in granules containing a core, inner

layer, and outer layer as in Japanese Kokai Patent Application No. Hei 8[1996]-92071. The coated granules described above can be prepared by any conventional method such as extrusion granulation, dry granulation, etc.

[0029]

Even in terms of pH, the preparations of the present invention do not form precipitates. During dissolution, at slightly alkaline pH, the calcium salt and sodium bicarbonate react to form insoluble precipitates, thus the preparations of the present invention are prepared by dissolution in a slightly acidic to neutral pH range. As a result, the preparations of the present invention can be obtained as concentrated fluids without the formation of precipitates.

[0030]

Effects of the invention

The preparations of the present invention can be made as 2-20% solutions without calcium salt precipitation, thus smaller dissolution baths can be used for dissolving the preparations, i.e., a smaller space can be used for dissolution in hospitals. Furthermore, with single-pack preparations, conventional dialysis fluid feeders can be used for dilution and the preparation of concentrated fluids can be simplified. For example, for conventional twin-pack powder dialysis agents, agents A and B have to be dissolved in separate tanks, while the dialysis agents of the present invention can be dissolved in one dissolution tank to obtain concentrated fluids. Thus, the number of dissolution tanks can be reduced and the dissolution operation simplified. In terms of operation, precise feed control of RO water, solution A and solution B is not necessary. Control of RO water and concentration of the concentrated fluid is sufficient for maintaining a constant balance of pH and electrolyte concentration. Thus, automation and further simplification are possible.

[0031]

With conventional single-pack bicarbonate dialysis agents, because of calcium carbonate precipitation, concentrated fluids can not be prepared, and 150-350 L of dialysis fluid are needed per dialysis per patient. It is practically impossible to prepare large amounts of dialysis fluids for many patients, and there are no advantages to single-pack bicarbonate dialysis agents.

[0032]

On the other hand, in the present invention, e.g., with concentrations of 10% or higher, the above volume can be reduced to less than 1/10, and existing commercial feed devices can be used without modification.

[0033]

The preparations of the present invention do not form insoluble salts during or after dissolution, and precipitates are not formed at all in lines feeding the diluted solutions for dialysis to patient's bedside (dialysis fluid feed line). Acetic acid washing frequency and acetic acid consumption for removing precipitates can be reduced greatly.

[0034]

The preparations of the present invention show excellent solubility and give uniform dialysis fluids even after being stored for a long period. Furthermore, since the preparations of the present invention are in powder form, great savings in transportation cost and storage space in hospitals are expected.

[0035]

With the dialysis fluids of the present invention, the citric acid in the dialysis fluid diffuses through the dialyzer, preventing blood coagulation inside the dialyzer, thus a reduction in the amount of blood coagulation prevention agents is expected.

[0036]

Application examples

Next, the present invention is explained in further detail with examples. However, the present invention is not limited to such examples.

[0037]

Application Example 1

The raw materials shown in Table 1 were used.

[0038]

Table 1

Sodium chloride	212.72 kg
Potassium chloride	5.22 kg
Calcium chloride	7.72 kg
Magnesium chloride	3.56 kg
Sodium citrate	20.59 kg
Glucose	35.00 kg
Citric acid	5.60 kg
Sodium bicarbonate	88.21 kg

Citrate ion:calcium ion = 2.8:1 (equivalent ratio)

First, sodium chloride and potassium chloride were mixed using a stir mixer, further mixed with an aqueous solution of calcium chloride and magnesium chloride (using 3.92 L of pure water) then with sodium citrate. The resulting mixture was dried in a tray type dryer at 160°C for about 6 h and sieved to obtain granules which were then compounded with glucose, citric acid and sodium bicarbonate to obtain a product. Of many products prepared, 5 were selected randomly and subjected to tests. Using 10.82 g of product treated with water to 1 L, ion concentrations were determined for Na^+ and K^+ with an atomic absorption photometer from Hitachi Seisakusho, Mg^{2+}, Cl^- and HCO_3^- with an ion chromatograph from Dionex Co., and Ca^{2+} by chelate titration, and citric acid and glucose with a liquid chromatograph from Hitachi Seisakusho. The results are given in Table 2.

[0039]

Table 2

Application Example 1 component test results (mEq/L)

	Na^+	K^+	Mg^{2+}	Ca^{2+}	Cl^-	HCO_3^-
Theoretical	140.0	2.00	1.00	3.00	110.0	30.00
n1	140.5	2.01	1.05	2.95	110.9	29.95
n2	140.2	2.01	1.02	3.04	110.1	29.57
n3	140.7	2.04	0.97	3.07	109.5	30.05
n4	139.1	2.02	0.99	2.96	110.2	29.96
n5	141.3	2.00	1.01	2.98	110.8	29.69
Average	140.4	2.02	1.01	3.00	110.3	29.92
SD	0.81	0.02	0.03	0.05	0.57	0.14

	citric acid	glucose
Theoretical	8.50	1.00 g/L
n1	8.47	0.99
n2	8.43	1.02
n3	8.48	0.97
n4	8.46	0.98
n5	8.48	0.99
Average	8.46	0.99
SD	0.02	0.02

[0040]

Application Example 2

The raw materials given in Table 3 were used.

[0041]

Table 3

Sodium chloride	207.60 kg
Potassium chloride	5.22 kg
Calcium chloride	7.72 kg
Magnesium chloride	3.56 kg
Sodium citrate	29.17 kg
Glucose	35.00 kg
Malic acid	5.87 kg
Sodium bicarbonate	88.21 kg

Citrate ion:calcium ion = 2.8:1 (equivalent ratio)

First, sodium chloride and potassium chloride were mixed using a stir mixer, further mixed with an aqueous solution of calcium chloride and magnesium chloride (using 3.92 L of pure water) then with sodium citrate. The resulting mixture was dried in a tray type dryer at 160°C for about 6 h and sieved to obtain granules which were then compounded with glucose, malic acid and sodium bicarbonate to obtain a product.

[0042]

Application Example 3

The raw materials given in Table 4 were used.

[0043]

Table 4

Sodium chloride	212.72 kg
Potassium chloride	5.22 kg
Anhydrous calcium gluconate	22.60 kg
Magnesium chloride	3.56 kg
Sodium citrate	20.59 kg
Glucose	35.00 kg
Citric acid	5.60 kg
Sodium bicarbonate	88.21 kg

Citrate ion:calcium ion = 2.8:1 (equivalent ratio)

First, sodium chloride and potassium chloride were mixed using a stir mixer, further mixed with an aqueous solution of magnesium chloride (using 1.42 L of pure water). The resulting mixture was dried in a tray type dryer at 160°C for about 6 h, mixed with 2.22 L of pure water, anhydrous calcium gluconate, then sodium citrate, dried at 80°C for about 6 h and sieved to obtain granules which were then compounded with glucose, citric acid and sodium bicarbonate to obtain a product.

[0044]

Comparative Example 1

The raw materials given in Table 5 were used.

[0045]

Table 5

Sodium chloride	212.72 kg
Potassium chloride	5.22 kg
Calcium chloride	7.72 kg
Magnesium chloride	3.56 kg
Anhydrous sodium acetate	17.23 kg
Glucose	35.00 kg
Malic acid	5.87 kg
Sodium bicarbonate	88.21 kg

Citrate ion:calcium ion = 2.8:1 (equivalent ratio)

First, sodium chloride and potassium chloride were mixed using a stir mixer, further mixed with an aqueous solution of calcium chloride and magnesium chloride (using 3.92 L of pure water) then with anhydrous sodium acetate. The resulting mixture was dried in a tray type dryer at 160°C for about 6 h and sieved to obtain granules which were then compounded with glucose, malic acid and sodium bicarbonate to obtain a product.

[0046]

Comparative Example 2

The raw materials given in Table 6 were used.

[0047]

Table 6

Sodium chloride	224.99 kg
Potassium chloride	5.22 kg
Calcium chloride	7.72 kg
Magnesium chloride	3.56 kg
Glucose	35.00 kg
Citric acid	5.60 kg
Sodium bicarbonate	88.21 kg

Citrate ion:calcium ion = 0.83:1 (equivalent ratio)

First, sodium chloride and potassium chloride were mixed using a stir mixer, further mixed with an aqueous solution of calcium chloride and magnesium chloride (using 3.92 L of pure water) then with sodium citrate. The resulting mixture was dried in a tray type dryer at 160°C for about 6 h and sieved to obtain granules which were then compounded with glucose, citric acid and sodium bicarbonate to obtain a product.

[0048]

Comparative Example 3

The raw materials given in Table 7 were used.

[0049]

Table 7

Sodium chloride	212.7 g
Potassium chloride	5.2 g
Calcium chloride	7.7 g
Magnesium chloride	3.6 g
Anhydrous sodium acetate	17.2 g
Glucose	35.0 g
Acetic acid	4.2 g
Total	285.6 g

Next, the characteristics of the preparations of the present invention are explained in further detail by comparing Application Examples 1-3 of the present invention with Comparative Example 1 and 2. First, the stability test results of the powders are given in Table 8. The preparations of Application Examples 1-3 and Comparative Examples 1-2 were filled in aluminum bags, heat-sealed, and stored at 40°C (RH 75%). Then, the pH was measured using the

F-13 pH meter from Horiba Seisakusho, and the 5-hydroxymethylfurfural absorbance (5-HMF abs) was measured at 284 nm using the U-3210 spectrophotometer from Hitachi Seisakusho.

[0050]

Table 8

		① 開始時	40℃(RH75%) ×1週間	40℃(RH75%) ② ×4週間
③	実施例1 pH (1.08g→100ml)	7.32	7.33	7.32
	⑤ 最大溶解濃度 (%)	15	15	15
	5-HMF Abs (5%溶液) ⑥	0.0041	0.0044	0.0050
	実施例2 pH (1.09g→100ml)	7.32	7.33	7.33
	⑤ 最大溶解濃度 (%)	15	15	15
	5-HMF Abs (5%溶液)	0.0087	0.0110	0.0117
	実施例3 pH (1.12g→100ml)	7.34	7.35	7.35
	⑤ 最大溶解濃度 (%)	15	15	15
	5-HMF Abs (5%溶液)	0.0080	0.0101	0.0121
④	比較例1 pH (1.07g→100ml)	7.32	7.33	7.33
	⑤ 最大溶解濃度 (%)	4	2	2
	5-HMF Abs (5%溶液)	0.0095	0.0126	0.0147
	比較例2 pH (1.06g→100ml)	7.33	7.50	7.65
	⑤ 最大溶解濃度 (%)	6	2	2
	5-HMF Abs (5%溶液)	0.0042	0.0192	0.0231

Key: 1 Initial
2 Weeks
3 Application Example ___
4 Comparative Example ___
5 Max. Concentration (%)
6 (5% solution)

In Application Examples 1-3 using sodium citrate, 15% solutions could be prepared with long-term storability; powder storability was good; no pH fluctuation occurred; good glucose stability was obtained. On the other hand, in Comparative Examples 1 and 2 without using sodium citrate, the maximum concentration was low; especially in Comparative Example 2, pH elevation and glucose degradation were substantial.

[0051]

Next, preparations from Application Examples 1-3 were made into 15% solutions, diluted to dialysis fluid concentration and measured for pH. Results are given in Table 9.

[0052]

Table 9

(1)	实施例1	实施例2	实施例3
(2) 透析液浓度pH	7.36	7.38	7.38

Key: 1 Application Example
2 Dialysis fluid pH

As shown above, at dialysis fluid concentration, the pH was within the desirable range of 7.2-7.4, showing that the preparations of the present invention can be made into 15% solutions, then diluted to desired concentrations.

[0053]

Next, a dissolution test was carried out for Application Example 1 and Comparative Example 3.

[0054]

The dissolution test of Application Example 1 was carried out by observing 1-15% solutions.

[0055]

In Comparative Example 3, 8.2 g of the mixed powder of Table 8 and 2.5 g of sodium bicarbonate were used to make 1-6% solutions which were observed.

[0056]

The results are shown below.

[0057]

Comparative Example 3

1%: clear, stable for more than 24 h

2%: turbid after 4 h

4%: turbid after 1 h

6%: turbid at dissolution

Application Example 1

1%: clear, stable for more than 24 h

2%: clear, stable for more than 24 h

4%: clear, stable for more than 24 h
6%: clear, stable for more than 24 h
10%: clear, stable for more than 24 h
15%: clear, stable for more than 24 h

As shown above, in Application Example 1, clarity is maintained for more than 24 h in the concentration range of 1-15%, while in the comparative example, precipitates were formed within a short time at a concentration of 2% or above. Comparative Example 3 is a typical twin-pack bicarbonate dialysis agent formulation, and when powders are dissolved individually, solutions are stable, but dissolving in one liquid at high concentration is not possible.

[0058]

Finally, in forming dialysis solutions using the preparation obtained in Application Example 1, the pH variation at dissolution is shown in Figure 1.

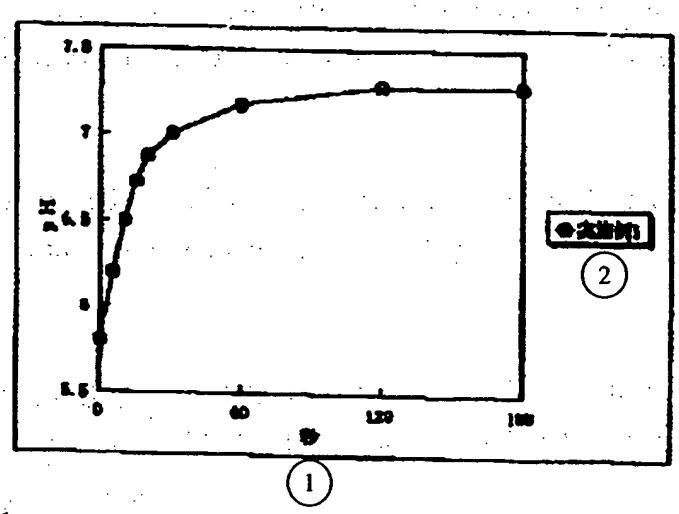
[0059]

The figure shows that this preparation is dissolved with a gentle elevation of pH in the weakly acidic to neutral pH range. Within this pH range, insoluble carbonate salt formation during dissolution is very difficult.

Brief description of the figure

Figure 1 is a graph illustrating the change in pH during dissolution when a dialysis solution is prepared from the preparation obtained in Application Example 1.

Figure 1



Key: 1 Seconds
2 Application Example 1